PB86-134699

Health Effects Assessment for Selenium (and Compounds)

(U.S.) Environmental Protection Agency
Cincinnati, OH

Sep 84

U.S. Department of Commerce
National Technical Information Service
NTIS

PB86-134699

EPA/540/1-86/058
September 1984

HEALTH EFFECTS ASSESSMENT FOR SELENIUM (AND COMPOUNDS)

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
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Washington, DC 20460

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NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
EPA/540/1-86/058		PB86 134699/AS

4. TITLE AND SUBTITLE	5. REPORT DATE
Health Effects Assessment for Selenium (and Compounds)	September 1984
	6. PERFORMING ORGANIZATION CODE: EPA/600/22
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Office of Emergency and Remedial Response Office of Solid Waste and Emergency Response U.S. Environmental Protection Agency Washington, DC 20460	13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A subchronic and chronic interim acceptable intake was determined for selenium (and compounds) based on oral exposure, and a chronic interim acceptable intake was determined based on inhalation exposure.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
Public	Unclassified	63
	20. SECURITY CLASS (This page)	22. PRICE
	Unclassified	

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with selenium (and compounds). All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Selenium. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-070. PB 81-117814.

U.S. EPA. 1983a. Reportable Quantity for Selenium (and Compounds). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The effects of oral selenium exposure have been studied relatively thoroughly in experimental animals and man. Evidence suggests that selenium is an essential element. An oral AIS of 0.224 mg/day and an oral AIC of 0.21 mg/day have been estimated based on animal and human data respectively. The AIC is in good agreement with NAS guidelines. A CS of 49 associated with increased neonatal mortality by oral exposure was calculated.

Data concerning inhalation effects of selenium are limited. Human data suggest an AIC of 0.07 mg/day for inhalation exposure. Data were inadequate to estimate an inhalation AIS.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

Editorial review for the document series was provided by:

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The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
EKG	Electrocardiogram
FAA	N-2-fluorenyl-acetamide
GI	Gastrointestinal
GSH-Px	Glutathione peroxidase
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PCB	Polychlorinated biphenyl
ppb	Parts per billion
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selenium is an element belonging to Group VIA of the periodic table. Elemental selenium has a CAS Registry number of 7782-49-2. It exists in nature in several oxidation states: -2, 0, +4 and +6. Selected physical properties of a few environmentally significant selenium compounds are given in Table 1-1.

Both natural and anthropogenic emissions are sources of selenium in the environment; however, the anthropogenic sources far outweigh the natural sources of selenium in the atmosphere. The main natural sources of selenium in the atmosphere are continental dust flux and volcanic dust and gas flux (Lantzy and MacKenzie, 1979). Coal combustion and copper production constitute ~90% of the overall atmospheric anthropogenic sources of selenium. Glass manufacturing, selenium-recovery plants, burning of fuel oil, and refuse burning are the other important anthropogenic sources of selenium in the atmosphere (NAS, 1976).

A small fraction of selenium may exist in the gaseous state in the atmosphere; however, the predominant amount of atmospheric selenium is expected to be present in the particulate form (NAS, 1976). Although chemical reactions in the troposphere may cause speciation of selenium, these processes may not be directly responsible for the removal of atmospheric selenium. Removal of selenium from the atmosphere may occur primarily through wet and dry deposition (NAS, 1976). The atmospheric residence time of selenium is probably dependent on the particulate diameter of selenium in the atmosphere. It has been determined by Natusch et al. (1974) that selenium emitted from coal-fired power plants (the primary source of atmospheric selenium) remains most concentrated in the smallest respirable particles.

TABLE 1-1

Selected Physical Properties of a Few Selenium Compounds[a]

Element/Compound	Formula	Molecular Weight	Specific Gravity/Density	Water Solubility	Vapor Pressure (mm Hg)
Selenium hydride	H_2Se	80.98	2.004 for liquid at -41.5°C	3.77 g/100 mℓ at 4°C	760 at -41.1°C
Selenium	Se	78.96	4.81^{20}_{4} for hexagonal bluish gray metal	insoluble[b]	1 at 356°C
Cadmium selenide	CdSe	191.36	5.81^{15}_{4}	insoluble[b]	NA
Sodium selenite	$Na_2SeO_3 \cdot 5H_2O$	263.01	NA	soluble[b]	NA
Sodium selenate	Na_2SeO_4	188.94	3.213 g/cm³ at 17.4°C	84 g/100 mℓ at 35°C	NA
Selenium dioxide	SeO_2	110.96	3.95^{15}_{15}	38.4 g/100 mℓ at 14°C	1 at 157°C

[a]Source: Weast, 1980

[b]No further information regarding solubility of these compounds is available in Weast, 1980

NA = Not available

Therefore, the residence time of atmospheric selenium is expected to be a few hours to several days.

The fate of selenium in aquatic media is dependent on the pH and oxidation-reduction potential of water. Under anaerobic conditions or low pH or both, insoluble elemental selenium or metal selenide is formed. Under aerobic conditions or pH >6, water soluble selenite (SeO_3^{2-}) or selenate (SeO_4^{2-}) is formed. Sorption and coprecipitation of the soluble selenite and selenate onto hydrous iron and manganese oxide control the mobility of the soluble selenium species. In a reducing aquatic environment, volatile H_2Se may be formed. Microorganisms present in sediments in bodies of water may also convert selenium into volatile methylated products. The last two processes may cause mobilization of selenium from the aquatic to the atmospheric phase (Callahan et al., 1979). The bioconcentration factor for selenium in freshwater and marine fish is ~400 (Callahan et al., 1979).

The fate of selenium in soils is largely dependent on the pH and redox potential of the soil. In acidic and poorly aerated soil, heavy metal selenides are formed and exist in immobilized form in soil. In well aerated and alkaline soils, selenium may be converted to SeO_3^{2-} and SeO_4^{2-}. The selenites (SeO_3^{2-}) may be immobilized by adsorption or complexation or both with iron and maganese hydroxides. The selenates, however, may leach from soils into groundwater (NAS, 1976). Page (1981) detected selenium at a median concentration of 2.0 ppb in all of the groundwater samples collected from New Jersey.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

In a study of the GI absorption of selenium, Thomson and Stewart (1973) administered doses of ~5 μCi [^{75}Se] selenomethionine (≤5 μg selenium) by gavage to groups of 20 female Wistar rats. GI absorption ranged from 91-93%. Another group of 20 rats received intragastric (~5 μg) doses of [^{75}Se] selenite and GI absorption was estimated to range from 95-97%. Subsequently, Thomson et al. (1975) administered 5 μCi [^{75}Se] selenocystine or ~2 μCi [^{75}Se] selenomethionine to groups of 25 female Wistar rats by gavage. Each dose contained not more than 5 μg selenium. Estimated absorption factors from the GI tract were 81.1 and 86.4% for [^{75}Se] selenocystine and [^{75}Se] selenomethionine, respectively.

Thomson and Stewart (1974) measured GI absorption of selenium in three women aged 33, 21 and 25 years. While fasting, each received an oral dose of ~10 μCi [^{75}Se] selenite containing ≤10 μg Se. Calculated GI absorption rates for the women were 70, 64 and 44%, respectively, indicating variation in absorption of selenite selenium.

Currently, the concept of bioavailability is beginning to replace empirical estimates of GI absorption associated with trace elements and other nutrients. A biological endpoint, such as alleviation of an experimentally reproducible deficiency syndrome, is chosen, and various forms of a trace element are administered to test animals. The abilities of these test compounds to alleviate or protect against a deficiency syndrome, compared to the protective ability of a reference compound, are evaluated and the results are usually expressed as a percentage of the biological activity of the reference compound.

Young et al. (1982) reviewed factors affecting bioavailability (hence, presumably, uptake) of various forms of selenium in animals and humans. Dietary factors included the intake level of the element and its chemical form; the presence or absence of promotors or inhibitors such as ascorbic acid, phytate, fiber, sugars, fats and proteins; various mineral-mineral interactions and mineral-macronutrient interactions; type and degree of food processing; and the concomitant ingestion of certain drugs. They also suggested that physiological factors such as nutritional state, physiological states (growth, pregnancy, etc.) and pathological states can influence selenium utilization. Biological factors such as infectious agents or social factors such as dietary habits also affect selenium uptake.

Gabrielsen and Opstvedt (1980) compared the availability of three sources of selenium to restore GSH-Px activity in baby chicks, a particularly sensitive experimental biological system. The ability of equal quantities of selenium contained in fishmeal, soybean meal and selenomethionine to restore GSH-Px activity were 48, 18 and 78%, respectively, when compared to GSH-Px activity restoration resulting from an equal amount of selenium from sodium selenite. These data seem to indicate that selenium in selenomethionine is much more readily absorbed than selenium in fishmeal or soybean meal.

Apparent biological availability depends in part, on the biological endpoint chosen. Young et al. (1982) reviewed the data of Cantor et al. (1975a,b) summarized in Table 2-1. From these data it is clear that selenite is more effective than selenomethionine in protecting chicks from exudative diathesis but that selenomethionine is far more protective than selenite against pancreatic fibrosis, another manifestation of selenium deficiency in chicks. It is impossible from these data to determine which

TABLE 2-1

Comparison of Two Biological Endpoints to Determine Bioavailability of Selenium*

Selenium Compound	Criterion: Protection Against	
	Exudative Diathesis (bioavailability)	Pancreatic Fibrosis (%)
Selenite	100	100
Selenocystine	68-78	~100
Selenomethionine	18-61	~400

*Source: Young et al., 1982

of the selenium compounds tested was absorbed most completely. It can be concluded that bioavailability tests reflect factors affecting metabolism and action at the target as well as absorption.

Several studies of New Zealand women, summarized by Young et al. (1982), indicated that absorption of [^{75}Se] selenomethionine was greater (96%) compared to either [^{75}Se] selenite (80%) or [^{75}Se] selenomethionine (79%) in food. Young et al. (1982) administered [^{75}Se]-labeled selenite to chickens by gavage periodically during a 42-day growing period. The chickens were killed and the resulting [^{74}Se]-labeled chicken meat with or without additional selenium ([^{76}Se]labeled selenite) was fed to four volunteers. Those consuming the [^{74}Se]-labeled chicken meat received 13.4 µg selenium and absorbed 80±5%. Subjects who received the labeled chicken meat and added [^{76}Se] selenite ingested 71.6 µg selenium and absorbed 30±11%. Thomson and Stewart (1973) and Thomson et al. (1975) indicated that GI absorption of selenium from selenite and selenomethionine was >86% in rats. In humans, Thomson and Stewart (1974) showed that absorption of selenium as selenite was quite variable, but considerably less than the absorption in rats. Apparently, GI absorption of organic forms of selenium in humans is more complete than absorption of selenium as selenite.

2.2. INHALATION

Pertinent data regarding pulmonary absorption of selenium following inhalation exposure could not be located in the available literature. The report by Glover (1967) associating urinary excretion of selenium with levels of selenium in workroom air (Section 3.2.2.) is indicative of the absorption of selenium from the lung.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Selenium is an essential trace element in livestock (Underwood, 1977), rat and chicken (U.S. EPA, 1980a) nutrition and is probably also essential to human health (U.S. EPA, 1980a; Frost and Lish, 1975; Harr, 1978). Frost and Lish (1975) cited its possible role in preventing sudden infant death syndrome, coronary heart disease, arthritis and cancer and its ability to reduce the toxicity of other heavy metals, such as cadmium and mercury. Flohe et al. (1973) found that selenium was associated with human GSH-Px, supporting the essential role of selenium to human health. The NAS (1980) determined an adequate and safe range for selenium intake of 50-200 µg/day for an adult human.

Elementary selenium in any of its allotropic forms is virtually insoluble in water and reportedly harmless if ingested (Shapiro, 1973); however, other dietary constituents affect the toxicity of selenium compounds. Smith (1939) found that 10 ppm selenium was very toxic to rats when fed a 10% protein diet, but no signs of toxicity were noted when dietary protein was increased by an additional 20%.

Although the literature contains many references regarding the toxicity of selenium (Schroeder et al., 1970), few quantitative studies of subchronic oral toxicity of selenium compounds to humans or animals have been located that relate effects to dosages administered. The purpose of this document is to evaluate concisely only those studies that provide data useful for risk assessment.

Anspaugh and Robison (1971) stated that rats and dogs exposed to dietary levels of 5-10 µg selenium/g may be expected to show evidence of chronic selenium toxicity, such as liver atrophy or necrosis, cirrhosis and hemorrhage, and a marked and progressive anemia with very low hemoglobin values.

Vesce (1974) observed changes in endocrine glands, especially the ovaries, pituitary and adrenals, in guinea pigs exposed orally to 5-12.5 mg sodium selenide for two periods of 20 days each. No further descriptions of protocol were available for these studies.

Tinsley et al. (1967) concluded that a dose of 0.5 mg/kg bw/day seemed to be the threshold that would affect longevity in rats. The authors calculated that for a 200 g rat eating 10 g of feed/day, this intake constituted a dietary concentration of 10 ppm. Harr et al. (1967) reported that additions of 0.5-2 μg selenium/g of diet resulted in hepatomegaly in rats (duration of exposure not specified). Effects at the lower dietary levels were more pronounced when selenium was added to semi-purified rather than commercial diets, suggesting that interaction of selenium with other trace elements is important in maintaining health. Harr and Muth (1972) stated that the MED for liver lesions was 0.25 μg selenium/g and the MED for effects on longevity and lesions of the heart, kidney and spleen was 0.75 μg/g. In these studies, chronic liver lesions (bile duct and parenchymal hyperplasia) were more prevalent in rats fed an unsupplemented commercial diet than in those fed the purified (casein-cerelose) diet supplemented with selenium. Interpretation of these results is, therefore, difficult.

Halverson et al. (1966) fed weanling male Sprague-Dawley rats wheat based diets containing 1.6, 3.2, 4.8, 6.4, 8.0, 9.6 or 11.2 μg selenium (natural feedstuff and selenite)/g for 6 weeks. No effects were reported in rats on diets containing up to 4.8 ppm selenium. At the dietary level of 4.8 ppm selenium, a depression in growth rate was noted in rats receiving their selenium as selenite but not in rats receiving their selenium as

natural selenium in seleniferous wheat. At dietary levels ≥6.4 ppm, reduced feed intake, increased mortality, splenomegaly, increased pancreas size, reduced liver weight and anemia were reported. In this study the dietary level of 3.2 ppm selenium was designated a NOEL.

Frost and Lish (1975) administered a selenium-vitamin E combination by capsule to seven volunteers for a period of 10 weeks. Another group of seven volunteers received placebos. All 14 volunteers received placebos during a 1-week pretreatment observation period. Those receiving selenium received 0.5 mg Se/day for 3 weeks, 1.0 mg Se/day for the next 3 weeks and 2.0 mg Se/day for the remaining 4 weeks. The preparation presumeably contained 0.5 mg selenite selenium and 100 IU of d-alpha tocopherol acid succinate. Observations, which continued for another 6 weeks, consisted of weekly physical examinations and "a battery of laboratory [tests] designed to monitor vital organ function." No differences could be detected between the drug and placebo.

3.1.2. Inhalation. Pertinent data regarding subchronic inhalation exposure of humans or animals to selenium could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Chronic oral exposure of humans to toxic levels of selenium has occurred from well water or foodstuffs grown on seleniferous soils, particularly in South Dakota, Wyoming, Nebraska and the People's Republic of China. Additionally, it is expected that acute or chronic toxicity may occur as a result of people medicating themselves with over-the-counter selenium preparations in an attempt to prevent cancer.

Beath (1962) described symptoms of lassitude, total or partial alopecia, discoloration of the skin and loss of fingernails in several people exposed to well water containing 9 mg selenium/ℓ. Discontinued use of the contaminated water resulted in regrowth of the hair and nails and increased mental alertness. Assuming an intake of 2 ℓ of water/day, the well water resulted in these effects at an intake of 18 mg/man/day.

Smith et al. (1936) conducted an epidemiological study of chronic selenium toxicity in people living on seleniferous soil where animals had been diagnosed as having alkali disease. Clinical signs in these people included bad teeth, jaundice, chloasma, vertigo, chronic GI disease, dermatitis, changes in nails (unspecified), arthritis, edema (location unspecified), lassitude and fatigue. Analysis of foodstuffs in the diets of these affected people revealed an intake of selenium of 0.1-0.2 mg/kg/day. Nearly all urine samples of affected people contained measurable amounts of selenium and 45% of these samples contained 0.2-1.33 μg/mℓ. Urinary content >0.2 μg/mℓ correlated with severity of symptoms.

Yang et al. (1983) reported outbreaks of selenium intoxication in several villages in the Hubei Province of the People's Republic of China. In five villages in which severe outbreaks occurred (totalling 248 inhabitants) the average incidence was 49.2% with an incidence of 85.5% in the most severely affected village. Evacuation and the concomitant change in diet resulted in recovery. The cause of the selenosis appeared to be the presence of high levels of selenium in surface coal in the air, which was then leached from the coal into the soil and into surface and ground waters. The outbreak was apparently caused by the increased consumption of selenium accumulating vegetables such as corn and turnip greens. Drinking water was considered to contribute negligibly to the intake of selenium.

Symptoms observed included brittleness of nails, loss of nails and hair, pruritis of the scalp, dermatitis characterized by hyperemia, edema and eruptive blistering, and nervous symptoms such as peripheral anesthesia, acroparesthesia and pain in the limbs. Eventually, exaggerated tendon reflexes, numbness, convulsions, motor dysfunction progressing to paralysis and hemiplegia developed. Mottled teeth and increased tooth decay were also reported, but interpretation of these findings is difficult because the area was also found to be high in fluoride. These symptoms correlated with daily intakes of selenium ranging from 3.20-6.69 mg/day with an average of 4.99 mg/day, computed based on analysis of components of the diet.

An increase in the incidence of dental caries has been associated with toxic levels of selenium in humans. Hadjimarkos and Bonhorst (1961) and Hadjimarkos (1969) showed that urinary excretion of selenium was about twice as high in children with a high incidence of dental caries compared with children with a low incidence of caries. Other studies have shown an inconsistent (Muhleman and Konig, 1964) or only marginally significant (Ludwig and Biddy, 1969) relationship between prevalence of dental caries and dietary levels of selenium. Unfortunately, no exposure data were available in the secondary source (U.S. EPA, 1980a) from which these studies were summarized. An increased incidence of dental caries has been observed in children in seleniferous communities where urine selenium levels averaged 0.33 mg/ℓ (Tank and Storvick, 1960). Bowen (1972) exposed young monkeys, Macaca irus, to drinking water containing 1 ppm selenium as sodium selenite for 5 years. Carious lesions developed twice as frequently and 3 times faster in the selenium-treated monkeys as in the control group. Assuming monkeys weigh 3.5 kg and drink 450 mℓ of water/day, 1 ppm selenium in the drinking water corresponds to an intake of 0.13 mg selenium/kg/day. Buttner

(1963) reported a positive correlation of dietary selenium with dental caries in rats. It is easier to control dietary factors in laboratory rats than in human populations, however, and other dietary factors may have been related to the incidence of dental caries in humans.

Several studies of chronic oral exposure of laboratory animals to selenium have been conducted. Franke and Potter (1935) fed groups of nine Wistar rats diets containing 0, 22.3 or 33.5 ppm selenium as sodium selenite. At 33.5 ppm selenium in the diet, decreased food consumption and growth and increased mortality (8/9 dead by day 359) were observed. At 22.3 ppm selenium in the diet, growth depression and increased mortality (5/9 dead by day 359) were noted. Necropsy of low-dose survivors revealed marked evidence of liver necrosis and degeneration.

Nelson et al. (1943) fed diets containing 0 or 10 ppm added selenium as ammonium potassium selenide to groups of 18 rats for 24 months. Excessive mortality (6/18 of controls, 12/18 of treatment rats) was reported.

Schroeder (1967) and Schroeder and Mitchener (1971a) treated groups of ~100 Long-Evans BLU:LE rats with drinking water containing no added selenium (controls), 2-3 mg/ℓ of sodium selenite or 2-3 mg/ℓ of sodium selenate. The experiment was intended to continue throughout the lifespan of the treated animals as a carcinogenicity bioassay. Male rats were especially sensitive to selenium as selinite and 50% of the males in the selenite group had died within 2 months. The remaining males in this group were given sodium selenate for the remainder of the experiment. Females in the selenite group were not similarly affected and remained on the sodium selenite treatment. No other parameters of toxicity were reported.

Fitzhugh et al. (1944) fed diets containing 5 ppm selenium as seleniferous corn in a relatively protein-deficient diet to rats for 24 months.

After 2 months and 1 year, respectively, mortality was 0 and 11% in the control rats and 11 and 17% in the treated rats. Although mortality in the treated rats after 1 year did not appear to differ significantly from mortality among control rats, after 2 months the incidence of mortality was much higher among treated rats compared with controls. Since a high protein diet provides partial protection against selenium toxicity (Smith, 1939), these data suggest that the ability of a low protein diet to exacerbate toxicity of selenium may be manifested more during the period of maximal growth when dietary requirements for protein are high, rather than after maturity.

Concurrently, Fitzhugh et al. (1944) fed rats diets containing 10, 20 or 40 ppm selenium as ammonium potassium selenide. The incidence of mortality, liver cirrhosis and liver tumors was increased in all treated rats compared with controls. The authors concluded, however, that selenide selenium was only half as toxic as an equivalent dose of selenium from seleniferous corn.

As mentioned previously, higher intakes of selenium have been associated with an increased incidence of dental caries. In an unpublished experiment reported by Frost and Lish (1975), selenium was given to monkeys by capsule at 0, 20, 64 or 200 μg/Kg/day. The preparation contained 0.5 mg selenium as the selenite and 100 IU vitamin E as d-alpha tocopherol acid succinate. After treatment for 55 weeks, three males and two females from each group were sacrificed for macro- and microscopic pathological examinations. The remaining monkeys were treated until week 58 and were sacrificed at week 70. Physical examinations, behavioral observations, survival and body weight gains, EKG and blood pressure determinations, ophthalmologic examinations, gross and microscopic pathological examinations, absolute and relative organ weights and a host of clinical chemistry and hematology parameters failed to reveal any signs of toxicity.

3.2.2. Inhalation. Hamilton (1974) reported chronic toxicity in workers due to occupational exposure to selenium. Symptoms including a strong garlic odor to the breath, sweat and urine, upper respiratory and GI irritation, cold-like symptoms, lacrimation and a metallic taste in the mouth were reported by workers exposed to selenium in a copper refinery. Hamilton (1974) also reported other cases of selenium toxicity related to industrial exposure; however, the level of exposure was not quantitated in any of these reports.

Belles (1981) suggested that selenium dioxide may be responsible for toxicity in industrial exposures. It is probably formed from heating selenium, and then forms selenious acid in water or sweat. The acid is irritating and was probably the cause for the evacuation of all workers and the hospitalization of two who experienced severe headache and respiratory discomfort as a result of exposure to fumes from an aluminum smelting operation that had been charged with selenium-contaminated, used rectifier plates (Clinton, 1947).

Glover (1967) measured urinary selenium concentration in workers at a selenium rectifier plant over a 5-year period. Workers were exposed to selenium in air at concentrations that varied with the particular process in which they were employed. Although the air concentrations were analyzed only sporadically, there seemed to be a correlation between air concentrations and urinary concentrations of selenium. Workers exposed to undetermined levels of airborne selenium complained of skin rashes (contact dermatitis), garlic odor of the breath, indigestion and indefinite sociopsychological effects. Although data were few, mortality among the selenium exposed workers did not appeared to be different from mortality among the

general population. Glover (1967, 1970) recommended a maximum allowable urinary concentration of selenium of 0.1 mg/ℓ, which he believed to correspond approximately to an air concentration of 0.1 mg/m³.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Although no reports conclusively link teratogenicity of selenium or its compounds to humans, Robertson (1970) suggested that selenium may be a teratogen in man. Rosenfeld and Beath (1964) suggested that malformed infants of Indian women in Colombia may have resulted from ingesting grains containing "toxic" levels of selenium. Robertson (1970) evaluated information on the possible association between abnormal pregnancies and exposure of women to selenite. Of one possible and four certain pregnancies studied, one went to term and resulted in a bilateral clubfoot infant. No information on the other pregnancies was available.

The chicken embryo is extremely sensitive to selenium. Hatchability of eggs is reduced by dietary concentrations of selenium too low to cause toxicity in other farm animals. The eggs are fertile but often produce grossly deformed embryos lacking eyes and beaks and having deformed wings and feet (Carlson et al., 1951; Franke et al., 1936; Franke and Tully, 1935; Gruenwald, 1958; Palmer et al., 1973). Deformed embryos were also produced by injection of selenite into the air cell of normal, fertile eggs of both chickens (Franke et al., 1936) and turkeys (Carlson et al., 1951).

The consumption of seleniferous diets by rats (Franke and Potter, 1935; Rosenfeld and Beath, 1964), pigs (Wahlstrom and Olson, 1958), sheep (Rosenfeld and Beath, 1964) and cattle (Dinkel et al., 1963) has been shown to interfere with normal fetal development and to cause fetal malformations.

These malformations are a part of the total syndrome designated "alkali disease" and, in general, seem to occur at dietary levels that cause other toxic manifestations (Underwood, 1977). These reports are not useful in risk assessment because no exposure data were given.

In an attempt to shorten the time involved in testing the chronic toxicity of chemicals, Schroeder and Mitchener (1971b) performed a multigeneration reproduction experiment in rats and mice using trace elements and other metals with known toxicity. Groups of five pairs of Charles River CD mice were fed a purified diet containing minimal (0.056 ppm) selenium. Treatment, initiated at weaning, was by the addition of 3 ppm selenium (as selenate) to doubly deionized drinking water. Control mice received the same diet and doubly deionized drinking water. Pairs of mice were allowed to breed to 6 months of age. The next generation was bred from F_{1a}, F_{1b} and F_{1c} offspring. The F_3 generation was obtained from F_{2a} and F_{2b} litters. The experiment was terminated when it was obvious that the strain was dying out or when the 3rd generation had been weaned.

Parameters of toxicity evaluated were intervals between litters, age at which first litter was produced, sex ratio at birth, number of runts, number of stillborn, failure to breed sucessfully, congenital abnormalities and maternal death. By these criteria, selenium was toxic to mice. The strain began to die out at the 3rd generation; seven pairs failed to breed; three that delivered produced a total of 23 offspring of which 16 were runts. In all, selenium in mice resulted in 93 runts of 389 offspring delivered live, one stillborn litter, death of 23 offspring shortly after birth, a male to female ratio in individual offspring ranging from 1.27-1.65 and one maternal death. Congenital malformations were not reported for selenium.

3.3.2. Inhalation. Studies associating teratogenicity with inhalation exposure to selenium could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Interactions between selenium and several toxic heavy metals have been demonstrated. Moxon (1938) alleviated the toxicity associated with 15 ppm dietary selenium (seleniferous grain, selenite or selenocystine) by providing 5 mg arsenic as sodium arsenate/ℓ of drinking water. The presence of arsenic appeared to enhance excretion of selenium into the GI tract (Ganther and Baumann, 1962), at least in part by increasing biliary excretion (Levander and Baumann, 1966). Presumably, administration of selenium could protect against toxicity induced by arsenic.

Selenium has been shown to protect against the toxic effects of cadmium upon various reproductive organs of rats. Kar et al. (1960) and Mason and Young (1967) demonstrated that testicular damage due to cadmium could be prevented by the simultaneous administration of selenium. Kar et al. (1959) and Parizek et al. (1968) found that selenium would prevent cadmium-induced damage to the non-ovulating ovary in the rat. Parizek et al. (1968) and Parizek (1964) found that administration of selenium prevented placental necrosis caused by exposure to small amounts of cadmium near parturition. The teratogenicity associated with cadmium and arsenic has been reduced by selenium (Holmberg and Ferm, 1969; Ferm, 1972). Parizek et al. (1968) and Gunn et al. (1968) greatly reduced the mortality rates of rats exposed to lethal doses of cadmium by the simultaneous administration of selenium.

Selenium salts have been shown to protect the kidney and intestines of rats exposed to lethal doses (0.02 mmole/kg) of mercury (Levander and Argrett, 1969). [The protective effects of selenium appeared to be associated with decreased urinary excretion of mercury (Parizek et al., 1971).]

Levander and Argrett (1969) reported that mercury increased the retention of selenium in the blood, kidneys and spleen. Parizek et al. (1971) found that transplacental movement of mercury in pregnant rats was decreased by selenium and in lactating rats less mercury was secreted into the milk. Also, the bioavailability of selenium in rats was reduced by mercury.

Diplock (1976) and Grasso et al. (1969) produced toxic symptoms in rats and chickens fed vitamin E-deficient diets with 0.15% silver acetate in the drinking water. Rats suffered dystrophic lesions and necrosis of the liver, and high mortality; chickens suffered a pro-exudative diathesis effect. Supplementation with the addition of 1 ppm selenium to the diet resulted in 55% protection against the toxic effects of silver. Liver lesions due to silver toxicity, and vitamin E and selenium toxicity were similar (Grasso et al., 1969).

Hollo and Sztojcso (1960) demonstrated that death due to thallium poisoning could be prevented by parenteral administration of selenate. Rusiecki and Brzezinski (1966) found that oral administration of selenate prevented thallium toxicity and resulted in a greater thallium content in liver, kidney and bone than occurred in nonselenate-treated animals subjected to thallium toxicity. Levander and Argrett (1969) showed that subcutaneous injection of thallium acetate increased the retention of selenium in the liver and kidney of rats and reduced pulmonary and urinary excretions of selenium.

Halverson and Monty (1960) demonstrated that dietary sulfate restored by >40% the growth rate depression in rats resulting from excessive dietary selenium as selenate or selenite. Sulfate, however, appeared to have no protective effect on liver degeneration associated with selenium.

Moxon and Dubois (1939) reported that fluoride increased the toxicity of selenium in rats. Adding 5 mg fluoride/ℓ to the drinking water of rats receiving 11 ppm dietary selenium as seleniferous grain resulted in increased mortality and decreased feed and water intake and rate of body weight gain. Hadjimarkos (1965, 1969), on the other hand, exposed rats to 3 mg selenium/ℓ of drinking water with and without the addition of 3 mg fluoride/ℓ of drinking water. No additional severity of toxicity was observed in the group receiving both selenium and fluoride.

Levander (1982) mentioned interactions between vitamin E and selenium. Several experiments show that these two nutrients can partially spare one another. For example, 0.05 ppm of dietary selenium was needed to prevent exudative diathesis in chicks fed a diet devoid of vitamin E, but only 0.01 ppm was needed when the diet contained 100 ppm vitamin E (Scott et al., 1967).

The herbicide, paraquat, is thought to be toxic as a result of stimulating lipid peroxidation (Bus et al., 1974). Cagen and Gibson (1977) found that, when exposed to toxic amounts of paraquat, selenium-deficient rats suffered increased lung damage and selenium-deficient mice suffered increased hepatic injury, compared with control animals that were not deficient in selenium.

Combs and Scott (1975) demonstrated that the addition of 50 ppm of PCB to the diets of chicks deficient in vitamin E and marginal in selenium resulted in an increase in the incidence of exudative diathesis compared with the incidence in chicks on similar diets without added PCB.

Selenium deficiency appears to protect against toxicity from certain xenobiotics. Burk and Lane (1979) observed that selenium deficient rats suffered less severe hepatotoxicity than selenium-adequate rats when exposed to acetaminophen or iodipamide.

Since under certain conditions cyanide inhibited the activity of GSH-Px (Kraus and Ganther, 1980), it was suggested that cyanide may precipitate selenium deficiency. Rudert and Lewis (1978) showed that drenching with potassium cyanide did increase the incidence of myopathy, a common manifestation of selenium deficiency in lambs. Selenium toxicity in rats has been alleviated by cyanide (Palmer and Olson, 1979), and linseed meal, long known to counteract selenium poisoning, has been shown to contain two cyanogenic glycosides (Palmer et al., 1980).

4. CARCINOGENICITY

4.1. HUMAN DATA

Evidence of a carcinogenic role for selenium in humans appears to be lacking. Although the occupational toxicity of selenium has been recognized since the early 1900s, no cases of malignancy attributable to exposure to the element have been reported (Schroeder et al., 1970). Shamberger and Frost (1969) cite data suggesting that selenium may help protect the human population against cancer. In a 31 state area in which forages grown for livestock consumption averaged $\leq$0.06 ppm, the death rate in 1965 was lower than in a 17 state area and the District of Columbia, in which forages averaged $\leq$0.05 ppm. In a study of the concentration of selenium in the blood and the death rate due to cancer, a nearly perfect negative Pearson coefficient ($r=-0.96$, $p<0.001$) was found, indicating that protection from death due to cancer is associated with higher blood levels of selenium (Shamberger and Frost, 1969).

In a review of selenium and cancer, Shapiro (1972) cited *in vitro* data suggesting an anticancer role for selenium. In experimental therapy in humans, Weisburger et al. (1956) and Weisburger and Suhrlaud (1956a,b) applied selenium cysteine in the treatment of cysteine-dependent leukemias. Chemical progress was impressive, but therapy was terminated due to selenium toxicity.

4.2. BIOASSAYS

Several investigators have studied the carcinogenicity of orally administered seleniferous compounds; however, none of these studies present reasonably consistent data that suggest a carcinogenic role for selenium.

After a short-term range finding experiment, Nelson et al. (1943) exposed seven groups of 18 female Osborne-Mendel rats to 5, 7 or 10 ppm selenium in the diet using either seleniferous corn or wheat. In addition, another 10 ppm selenium group was treated with selenite added to the diet. A control group of 18 rats was maintained. Mortality was high and tended to be proportional to the dietary level of selenium. Of 53 treated rats that survived to 18 months, 11 developed hepatocellular "adenomas or low grade carcinomas." Rats that died or were killed before 18 months exhibited cirrhosis starting as early as 3 months, but no tumors were found. The 14 control rats that survived to 18 months showed no evidence of neoplasia. There was no discussion of the statistical significance of these findings.

Harr et al. (1967) and Tinsley et al. (1967) assigned 1437 Wistar rats to 34 different dietary groups. Dietary selenium levels ranged from 0.5-16 ppm (sodium selenite and selenate) in rats maintained on high (22% casein) or low (12% casein with or without 0.3% DL-methionine) protein diets. A known carcinogen, FAA, was fed at dietary levels of 50 or 100 ppm to some groups as a positive control. Mortality claimed many rats in the 8 and 16 ppm groups and caused early termination of these groups. Most rats lived <100 days; 175 lived $\geq$2 years. Necropsies were performed on 1126 of the original 1437 rats; 63 neoplasms were found, 43 in FAA-exposed rats and the other 20 randomly distributed among selenium-treated animals. No hepatomas were found. Although lifetime exposures to toxic levels of selenium were shown to produce serious pathological changes in the liver and other organs, no hepatic cancers were observed among selenium-exposed animals. The total number of cancers observed and their distribution in treated rats appeared similar to those observed in controls.

Volgarev and Tscherkes (1967) reported the results of three experiments in which rats were fed diets containing variable levels of protein (12-30% casein) and selenium from selenate at 4.3 or 8.6 ppm. In the first experiment, 23/40 rats lived ≥18 months, 4 developed sarcomas, 3 hepatocellular carcinomas and 3 hepatocellular adenomas. Two of the rats with hepatocellular carcinomas had metastases. In the second experiment involving 60 rats, one hepatocellular carcinoma, one hepatocellular adenoma and three sarcomas were reported. Preneoplastic lesions or carcinomas were not reported in the third experiment with 100 rats. Negative control rats were not included in these experiments; hence, no conclusions can be made regarding the incidence of these observed tumors.

Schroeder (1967) and Schroeder and Mitchener (1971a) exposed 418 weanling Long-Evans rats to 2-3 mg of sodium selenite or sodium selenate, or 2 mg tellurite/ℓ of drinking water for lifetime. At 21 months of age, a virulent epidemic of pneumonia caused considerable mortality. Necropsy of ~75% of the animals was performed at ~28 months. Histological examinations were performed only on selected individuals. Control animals exhibited 11 malignant tumors and 20 were reported in the selenate-exposed rats. No statistical analyses of these data were reported. Few data regarding malignancies in the selenite-exposed groups were given. Due to the toxicity of selenite, male rats were switched to selenate and, along with the females on selenite, were terminated before the age of high tumor incidence.

Schroeder and Mitchener (1972) repeated these studies in mice. Treatment of 3 mg selenium/ℓ of drinking water did not have a significant effect on the incidence of spontaneous tumor formations in mice.

The U.S. EPA (1980a) reported the unpublished results of an NCI (1978) bioassay. B6C3F1 mice were divided into groups of 50 of each sex and were designated control, vehicle control, low-dose and high-dose groups.

Low- and high-dose groups received 11.05 mg selenium/kg and 55.24 mg selenium/kg, respectively, as selenium disulfide in carboxymethyl cellulose by gavage for lifetime. It was apparent that this strain of mice had a high rate of spontaneous tumors of multiple anatomic sites. Among groups of male mice, exposure to selenium did not result in any statistically significant increased incidence of tumors. High-dose females, however, experienced a significantly higher (21/49) incidence of hepatocellular carcinoma compared with controls (2/50) or vehicle controls (0/49).

These data suggest that, at least in female mice, selenium disulfide is a carcinogen. Selenium disulfide, however, is not just another salt of selenium but a distinct compound which is unlikely to be found in the environment as a pollutant. It cannot be assumed that these results suggest that inorganic selenium (selenite or selenate) would be carcinogenic in humans or animals (U.S. EPA, 1980a).

4.3. OTHER RELEVANT DATA

Recent data concerning the mutagenicity of selenium or its compounds could not be located in the available literature. The U.S. EPA (1980a) has summarized the data to 1980, which is presented here.

Selenium in selenoamino acid has been shown to reduce genetic crossing over in Drosophila melanogaster. Selenocystine at 2 mmol had a significant effect on crossing-over in the x-chromosome of D. melanogaster (Ting and Walker, 1969; Walker and Bradley, 1969).

Sentein (1967) found that selenates, selenites and selenium dioxide caused similar effects on segmentation mitoses: polar dissociation with conserved dominance of the principal pole, stickiness and chromosomal clumping. In another study, sodium selenite was found to cause degenerative cell changes and decreased mitotic activity in rabbit kidney tissue cultures (exposure unspecified) (Fokina and Kudryavtseria, 1969).

No chromosomal aberrations were observed in human leukocyte or fibroblast cultures exposed to at least two concentrations of sodium selenate or sodium selenite for 24, 48 or 72 hours (Paton and Allison, 1972).

4.4. WEIGHT OF EVIDENCE

From the studies reviewed in Section 4.2., it is apparent that the carcinogenicity of inorganic selenium has not been unequivocally established and the question of the carcinogenicity of inorganic selenium will not be resolved without further investigation. There is limited evidence, however, that selenium disulfide is a carcinogen in female mice, but none of the studies to date provide a weight of evidence or sufficient dose-response data for risk estimation. The NAS (1976) mentioned that selenium salts have been used both prophylactically and therapeutically in livestock husbandry for a number of years. Human exposure to selenium has included its incorporation into shampoos and its presence in industrial plants. Epidemiologic and demographic evidence from its widespread use has failed to implicate selenium as a carcinogen; in fact, it has been associated with a reduction in the incidence of human ovarian cancer (Frost, 1971; Schroeder and Mitchener, 1972; Anonymous, 1970; Shamberger and Rudolph, 1966; Shamberger et al., 1972, 1973; Shamberger and Willis, 1971; Wedderburn, 1972).

Several studies have demonstrated an inhibitory effect on tumor incidences in laboratory animals, complicating assessment of the carcinogenic role of selenium. Harr et al. (1972) noted an apparent decreased incidence of 2-acetylaminofluorene-induced mammary carcinomas and hepatomas in mice related to content of selenium in the diet. A 50% reduction in the incidence of dimethylaminobenzene-induced liver tumors in rats was noted as the result of adding 5 ppm sodium selenite to the diet (Clayton and Baumann, 1949).

IARC (1975) concluded that the available animal data are insufficient for evaluation of the carcinogenicity of selenium compounds. The available human data do not suggest that selenium is carcinogenic in man, and "the evidence for a negative correlation between regional cancer deaths and selenium is not convincing" (IARC, 1975). Applying the criteria for evaluating the overall weight of evidence for the carcinogenicity of selenium (and compounds) for humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), selenium is most appropriately designated a Group D - Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1980) recommended a TWA-TLV for selenium in the workroom atmosphere of 0.2 mg/m^3, primarily to protect against the irritative effects of selenium. No STEL has been recommended. The ACGIH (1983) recommended a TWA-TLV of 0.2 mg/m^3 selenium for selenium hexafluoride. The OSHA standard for selenium has been set at 0.2 mg/m^3 (Code of Federal Regulations, 1981).

The U.S. EPA (1980a) concluded that the carcinogenicity of selenium has not been clearly demonstrated, and based the derivation of an ambient water quality criterion on the collective data of several short-term toxicity studies in rats. Based on an estimated LOEL in rats, occurring at 0.5 ppm selenium in the diet, the U.S. EPA (1980a) recommended an ambient water quality criterion of 10 µg/ℓ. This value was chosen with the consideration that only 5-10% of the daily exposure to selenium should come from ingestion of water.

The FDA ruled that sodium selenite or sodium selenate may be added to the complete feed for swine and chickens up to 16 weeks of age not to exceed 0.1 ppm, and for turkeys, not to exceed 0.2 ppm (U.S. EPA, 1980a).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Reports of toxicity in humans with subchronic oral exposure to selenium could not be located in the available literature. Animal data concerning subchronic oral selenium toxicity are difficult to interpret. Harr et al. (1967) reported hepatomegaly in rats associated with 0.5 ppm selenium in the diet. Harr and Muth (1972) suggested that a dietary level of 0.25 ppm was the threshold associated with liver lesions and that 0.75 ppm was related to reduced longevity; however, artificially contrived purified diets were used that circumvented the normal interactions of trace elements and resulted in unusual apparent toxicity associated with selenium, and these data must be interpreted with caution. Anspaugh and Robison (1971) demonstrated liver atrophy in rats and dogs, and Vesce (1974) found "endocrine changes" in guinea pigs exposed to diets containing 5 ppm selenium. Halverson et al. (1966) fed diets containing 1.6 (intrinsic), 3.2, 4.8, 6.4, 8.0, 9.6 or 11.2 ppm selenium to rats for 6 weeks. Dietary levels $\geq$6.4 ppm resulted in mortality, anemia and pathologic changes in liver, pancreas and spleen. A dietary level of 4.8 ppm was associated with reduced growth rate in some rats. In this study, 3.2 ppm selenium corresponding to an intake of 0.16 mg/kg bw/day, assuming rats eat food equivalent to 5% of their body weight/day, was a NOEL. From this animal dose, an AIS can be calculated by multiplying the animal dose (0.16 mg/kg bw/day) by 70 kg (body weight of man) and dividing by an uncertainty factor. The fact that selenium is a required nutrient for animals and presumably for humans (NAS, 1980) enters into the selection of an uncertainty factor. An uncertainty factor of 50 is chosen, a factor of 5 for interspecies extrapolation, because it seems reasonable that both rats and humans may have similar

dietary requirements for selenium (U.S. EPA, 1980a) and a factor of 10 to provide additional protection for especially sensitive populations, such as people living in known seleniferous areas. The resultant AIS = 0.224 mg/day for subchronic oral exposure. The NAS (1980) Food and Nutrition Board recommended a human dietary requirement of 10-200 µg/day for selenium and estimated that the average adult ingests ~130-150 µg of selenium/day from food.

6.1.2. Inhalation. Pertinent data regarding subchronic inhalation exposure of humans or laboratory animals to selenium could not be located in the available literature; hence, no interim AIS for subchronic inhalation exposure can be calculated.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. Beath (1962) reported symptoms of lassitude, alopecia, discoloration of skin, and loss of fingernails in people exposed to well water containing 9 mg selenium/ℓ. Assuming an intake of 2 ℓ of water/day, an average of ~18 mg selenium/man/day was ingested. Smith et al. (1936) examined the diets of people farming seleniferous soils and reported that average daily intakes of ~7-14 mg of selenium were associated with symptoms similar to those described by Beath (1962).

Several investigators (Franke and Potter, 1935; Nelson et al., 1943; Fitzhugh et al., 1944) chronically exposed laboratory animals to selenium by the oral route, but the exposures used resulted in mortality and did not define NOELs, NOAELs or LOAELs that are useful to risk assessment. More recently, however, Bowen (1972) exposed young monkeys for 5 years to drinking water containing 1 ppm selenium to study the impact of a low level of selenium on the formation of dental caries. Carious lesions developed twice as frequently and 3 times faster in selenium-treated monkeys than in control

monkeys. No other signs of selenium toxicity were reported. Assuming that monkeys weigh 3.5 kg and drink 450 mℓ water/day, an intake of 0.13 mg selenium/kg bw/day is calculated. That the dose of 0.13 mg/kg bw/day associated with increase in dental caries is below the threshold for other effects in monkeys is supported by the data reported by Frost and Lish (1975). In this study, no manifestations of toxicity were observed in monkeys given 200 µg/kg/day by capsule. Dental caries were not reported in this study at this dosage level but it is not clear whether an oral examination was performed and this study ran for a much shorter period of time than the 5-year study of Bowen (1972).

The epidemiology study of Yang et al. (1983) is chosen rather than the monkey study of Bowen (1972) for derivation of an ADI because the LOAEL from the human study, 3.20 mg/day or 46 µg/kg bw/day, is lower than the NOEL of 200 µg/kg bw/day from the monkey study. Furthermore, the effects were carefully catalogued and care was taken in estimating the range of intakes associated with selenosis. The uncertainties associated with animal to human extrapolation are also eliminated. The U.S. EPA (1985) derived an ADI for selenium based on the LOAEL of 3.20 mg/day associated with selenosis from the human epidemiological data (Yang et al., 1983). An uncertainty factor of 15 was applied to convert the LOAEL of 3.20 mg/day to an ADI. A factor of 15 rather than 10 was applied to reflect more efficient absorption from water than from the diet. An ADI of 0.21 mg/day was calculated for selenium. It is suggested that this ADI be adopted as the oral AIC. This ADI is similar to the ADI of 0.224 mg/day calculated for subchronic exposure from the Halverson et al. (1966) study in rats.

U.S. EPA (1983a) reviewed the data base for selenium and its compounds and selected the multigeneration study in mice (Schroeder and Mitchener, 1971b) as being most appropriate for calculating a CS to most stringently represent the toxicity of selenium compounds. Assuming that mice consume water equivalent to 17% of their body weight, an intake of 0.51 mg/kg bw/day was calculated. The animal dose was multiplied by the cube root of the ratio of the body weight of mice (assumed to be 0.03 kg) to that of humans (assumed to be 70 kg) and multiplied by 70 kg to derive a human MED of 2.69 mg/day. This MED corresponds to an RV_d of 4.9 and the effect observed, increased neonatal mortality, was assigned an RV_e of 10. The resulting CS, 49, was calculated as the product of RV_d and RV_e.

6.2.2. Inhalation. Glover (1967) measured urinary concentrations of selenium in workers exposed to atmospheric selenium and found that a urinary concentration of 0.1 mg/ℓ corresponded to an air concentration of 0.1 mg/m³, which he recommended as a maximum allowable concentration in workroom air. Lacking more definitive data on the effects of selenium by inhalation, an AIC can be derived from these data as from a TLV. Assuming a worker inhales 10 m³ of air during the workday, this exposure corresponds to a daily intake of 1 mg/day during a 5-day workweek. An AIC is calculated by multiplying by 5/7 to expand the exposure to a 7-day week and by dividing by an uncertainty factor of 10, intended to provide greater protection to members of the population unusually sensitive to selenium inhalation. The resultant AIC is 0.07 mg/day.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. Although the NCI (1978) bioassay indicated a possible carcinogenic role for selenium disulfide in female B6C3F1 mice, as was discussed in Section 4.4., the carcinogenicity of other selenium compounds

is uncertain at the present time. The U.S. EPA (1980a), suggesting that the currently available information does not warrant classification of selenium or its compounds as carcinogenic and reviewing the conclusion of the NAS (1976) that selenium intake may be correlated with a reduction in the incidence of cancer, concluded that insufficient evidence was available from which to calculate a q_1^*.

6.3.2. Inhalation. Since no reports of carcinogenicity associated with inhalation exposure to selenium or its compounds have been located in the available literature, no q_1^* for inhalation exposure can be calculated.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values for Substances in Workroom Air, 4th ed. with supplements through 1981. Cincinnati, OH. p. 361-362. (Cited in U.S. EPA, 1983a)

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1984. Cincinnati, OH.

Anonymous. 1970. Selenium and cancer. Nutr. Rev. 28: 75-80. (Cited in U.S. EPA, 1980a)

Anspaugh, L.R. and W.L. Robison. 1971. Trace elements in biology and medicine. Prog. Atomic Med. 3: 63. (Cited in U.S. EPA, 1980a)

Beath, O.A. 1962. The story of selenium in Wyoming. University of Wyoming, Laramie. (Cited in U.S. EPA, 1980a)

Belliles, R.P. 1981. Phosphorus, selenium and tellurium. In: Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. IIA, G.D. Clayton and F.E. Clayton, Ed. John Wiley and Sons, Inc., NY. p. 2130-2140.

Bowen, W.H. 1972. No title provided. J. Ir. Dent. Assoc. 18: 83. (Cited in Underwood, 1977; U.S. EPA, 1983a)

Burk, R.F. and J.M. Lane. 1979. Ethane production and liver necrosis in rats after administration of drugs and other chemicals. Toxicol. Appl. Pharmacol. 50: 467. (Cited in Levander, 1982)

Bus, J.S., S.D. Aust and J.E. Gibson. 1974. Superoxide- and singlet oxygen-catalyzed lipid peroxidation as a possible mechanism for paraquat (methyl viologen) toxicity. Biochem. Biophys. Res. Commun. 58: 749. (Cited in Levander, 1982)

Buttner, W. 1963. Action of trace elements on the metabolism of fluoride: J. Dent. Res. 42: 453. (Cited in U.S. EPA, 1980a)

Cagen, S.Z. and J.E. Gibson. 1977. Liver damage following paraquat in selenium-deficient and diethyl maleate-pretreated mice. Toxicol. Appl. Pharmacol. 40: 193. (Cited in Levander, 1982)

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-related environmental fate of 129 priority pollutants. Vol. I. U.S. EPA, Office of Water Planning and Standards, Office of Water and Waste Management, Washington, DC. EPA 440/4-79-029a.

Cantor, A.H., M.L. Scott and T. Noguchi. 1975a. Biological availability of selenium in feedstuffs and selenium compounds for restoring blood plasma glutathione peroxidase activity in selenium-depleted chicks. J. Nutr. 105: 96-105. (Cited in Young et al., 1982)

Cantor, A.H., M.L. Langevin, T. Noguchi and M.L. Scott. 1975b. Efficiency of selenium in selenium compounds and feedstuffs for prevention of pancreatic fibrosis in chicks. J. Nutr. 105: 106-111. (Cited in Young et al., 1982)

Carlson, C.W., et al. 1951. Some effects of selenium, arsenicals and vitamin B_{12} on chick growth. Poultry Sci. 33: 768. (Cited in U.S. EPA, 1980a)

Clayton, C.C. and C.A. Baumann. 1949. Diet and azo diet tumors; effect of diet during a period when the dye is not fed. Cancer Res. 9: 575. (Cited in U.S. EPA, 1980a)

Clinton, M., Jr.. 1947. Selenium fume exposure. J. Ind. Hyg. Toxicol. 29: 225.

Code of Federal Regulations. 1981. OSHA Safety and Health Standards. 29 CFR 1910.1000.

Combs, G.F., Jr. and M.L. Scott. 1975. Polychlorinated biphenyl-stimulated selenium deficiency in the chick. Poultry Sci. 54: 1152. (Cited in Levander, 1982)

Dinkel, et al. 1963. Effects of season of breeding on reproductive and weaning performance of beef cattle grazing seleniferous range. J. Anim. Sci. 22: 1043. (Cited in U.S. EPA, 1980a)

Diplock, A.T. 1967. Vitamin E and stress 3. The metabolism of D tocopherol in the rat under dietary stress with silver. Br. J. Nutr. 21: 115-125. (Cited in U.S. EPA, 1980a)

Federal Register. 1984. Environmental Protection Agency. Proposed guidelines for carcinogenic risk assessment. 49 FR 46294-46299.

Ferm, V.H. 1972. The teratogenic effects of metals on mammalian embryos. Adv. Teratol. 5:51.

Fitzhugh, O.G., A.A. Nelson and C.I. Bliss. 1944. The chronic oral toxicity of selenium. J. Pharmacol. Exp. Therap. 80: 289-299. (Cited in U.S. EPA, 1983a)

Flohe, L., et al. 1973. Glutathione peroxidase: A selenioenzyme. Fed. Eur. Biochem. Soc. Lett. 32: 132. (Cited in U.S. EPA, 1980a)

Fokina, A.M. and T.P. Kudryavtseria. 1969. Mikroelem med. Zhivotnovod, M. Kruming, Ed. USSR:Elm Baku. (Cited in U.S. EPA, 1980a)

Franke, K.W. and V.R. Potter. 1935. New toxicant occurring naturally in certain samples of plant foodstuffs; toxic effects of orally injected selenium. J. Nutr. 10: 213. (Cited in U.S. EPA, 1980a)

Franke, K.W. and W.E. Tully. 1935. A new toxicant occurring naturally in certain samples of plant foodstuffs. V. Low hatchability due to deformities in chicks. Poultry Sci. 14: 273. (Cited in U.S. EPA, 1980a)

Franke, K.W., et al. 1936. Monstrosities produced by injection of selenium salts into hens' eggs. Ant. Rec. 65: 15. (Cited in U.S. EPA, 1980a)

Frost, D.V. 1971. The case for selenite as a feed additive. Feedstuffs. 43: 12. (Cited in U.S. EPA, 1980a)

Frost, D.V. and P.M. Lish. 1975. Selenium in biology. Ann. Rev. Pharmacol. 15: 259.

Gabrielsen, B.O. and J. Opstvedt. 1980. Availability of selenium in fish meal in comparison with soybean meal, corn gluten meal and selenomethionine relative to selenium in sodium selenite for restoring glutathione peroxidase activity in selenium-depleted chicks. J. Nutr. 110: 1096-1100. (Cited in Young et al., 1982)

Ganther, H.E. and C.A. Baumann. 1962. Selenium metabolism. I. Effects of diet, arsenic, and cadmium. J. Nutr. 77: 210. (Cited in U.S. EPA, 1980a)

Glover, J.R. 1967. Selenium in human urine: A tentative maximum allowable concentration for industrial and rural populations. Ann. Occup. Hyg. 10: 3-10. (Cited in U.S. EPA, 1983a)

Glover, J.R. 1970. Selenium and its industrial toxocology. Ind. Med. Surg. 39:50.

Grasso, P., R. Abraham, R. Hendy, A.T. Diplock, L. Golberg and J. Green. 1969. The role of dietary silver in the production of liver necrosis in vitamin E-deficient rats. Exp. Mol. Pathol. 11: 186-199. (Cited in U.S. EPA, 1980a)

Gruenwald, P. 1958. Malformation caused by necrosis in the embryo illustrated by the effects of selenium compounds on chick embryo. Am. J. Pathol. 34: 77. (Cited in U.S. EPA, 1980a)

Gunn, S.A., T.C. Gould and W.A.D. Anderson. 1968. Mechanisms of zinc, cysteine and selenium protection against cadmium-induced vascular injury to mouse testis. J. Reprod. Fert. 15: 65-70. (Cited in U.S. EPA, 1980a)

Hadjimarkos, D.M. 1965. Effect of selenium on dental caries. Arch. Environ. Health. 10: 893-899. (Cited in U.S. EPA, 1980a)

Hadjimarkos, D.M. 1969. Selenium: A caries enhancing trace element. Caries Res. 3: 14. (Cited in U.S. EPA, 1980a)

Hadjimarkos, D.M. and C.W. Bonhorst. 1961. The selenium content of eggs, milk, and water in relation to dental caries in children. J. Pediatr. 59: 256. (Cited in U.S. EPA, 1980a)

Halverson, A.W. and K.J. Monty. 1960. An effect of dietary sulfate on selenium poisoning in the rat. J. Nutr. 70: 100. (Cited in U.S. EPA, 1980a)

Halverson, A.W., et al. 1966. Toxicity of selenium to postweanling rats. Toxicol. Appl. Pharmacol. 9: 477. (Cited in U.S. EPA, 1980a)

Hamilton, A. 1974. Industrial Toxicology. Harper, NY.

Harr, J.R. 1978. Biological Effects of Selenium. In: Toxicity of Heavy Metals in the Environment, F.W. Oehme, Ed. Dekker, New York. p. 393.

Harr, J.R. and O.H. Muth. 1972. Selenium poisoning in domestic animals and its relationship to man. Clin. Toxicol. 5: 175-186. (Cited in U.S. EPA, 1980a)

Harr, J.R. J.F. Bone, I.J. Tinsley, P.H. Weswig and R.S. Yamamoto. 1967. Selenium toxicity in rats. II. Histopathology. In: Selenium in Biomedicine, O.H. Muth, Ed. Proc. 1st Intl. Symp., Oregon State University, 1966. AVI Publishing Co., Westport, CT. p. 153-178. (Cited in U.S. EPA, 1980a)

Harr, J.R., et al. 1972. Effect of dietary selenium on N-2-fluorenylacetamide (FAA)-induced cancer in vitamin E supplemented, selenium depleted rats. Clin. Toxicol. 5: 187. (Cited in U.S. EPA, 1980a)

Hollo, M.Z. and Z. Sztojcso. 1960. Prevention of death by means of selenium salts administered before roentgen-irradiation. Borgyogy Vener Szenle. 36: 203. (Cited in U.S. EPA, 1980a)

Holmberg, R.E., Jr. and V.H. Ferm. 1969. Interrelationships of selenium, cadmium, and arsenic in mammalian teratogenesis. Arch. Environ. Health. 18: 873-877. (Cited in U.S. EPA, 1980a)

IARC (International Agency for Research on Cancer). 1975. Evaluation of Carcinogenic Risk of Chemicals to Man. Monograph No. 9. Lyon, France. (Cited in U.S. EPA, 1980a)

Kar, A.B., et al. 1959. Ovarian changes in prepubertal rats after treatment with cadmium chloride. Acta Biol. Med. Ger. 3. (Cited in U.S. EPA, 1980a)

Kar, A.B., et al. 1960. Prevention of cadmium-induced changes in the gonads of the rat by zinc and selenium: A study in the antagonism between metals in the biological system. Proc. Natl. Inst. Sci. India Part B, Suppl. 26. (Cited in U.S. EPA, 1980a)

Kraus, R.J. and H.E. Ganther. 1980. Reaction of cyanide with glutathione peroxidase. Biochem. Biophys. Res. Commun. 96: 1116. (Cited in Levander, 1982)

Lantzy, R.J. and F.T. MacKenzie. 1979. Atmospheric trace metals: Global cycles and assessment of man's impact. Geochim. Cosmochim. Acta. 43: 511-525.

Levander, O.A. 1982. Selenium: Biochemical actions, interactions, and some human health implications. In: Clinical, Biochemical and Nutritional Aspects of Trace Elements. Alan R. Liss, Inc., NY. p. 345-368.

Levander, O.A. and L.C. Argrett. 1969. Effects of arsenic, mercury, thallium, and lead on selenium metabolism in rats. Toxicol. Appl. Pharmacol. 14: 308-314. (Cited in U.S. EPA, 1980a)

Levander, O.A. and C.A. Baumann. 1966. Selenium metabolism. VI. Effect of arsenic on the excretion of selenium in the bile. Toxicol. Appl. Pharmacol. 9: 106. (Cited in U.S. EPA, 1980a)

Ludwig, T.G. and B.C. Biddy. 1969. Geographic variations in the prevalence of dental caries in the United States of America. Caries Res. 3: 32. (Cited in U.S. EPA, 1980a)

Mason, K.E. and J.O. Young. 1967. Effectiveness of selenium and zinc in protecting against cadmium-induced injury of the rat tests. In: Selenium in Biomedicine, O.H. Muth, Ed. Proc. 1st Intl. Symp., Oregon State University, 1966. AVI Publishing Co., Westport, CT. p. 383. (Cited in U.S. EPA, 1980a)

Moxon, A.L. 1938. The effect of arsenic on the toxicity of seleniferous grains. Science. 88: 81. (Cited in U.S. EPA, 1980a)

Moxon, A.L. and K.P. Dubois. 1939. Influence of arsenic and certain other elements on the toxicity of seleniferous grains. J. Nutr. 18: 447. (Cited in U.S. EPA, 1980a)

Muhleman, N. and K. Konig. 1964. Caries activity of male and female Osborne-Mendel rats in different environments. Helv. Odontol. Acta. 8: 79. (Cited in U.S. EPA, 1980a)

NAS (National Academy of Sciences). 1976. Selenium. Comm. Med. Biol. Effects, Environ. Pollut. Subcomm. Selenium, Washington, DC. (Cited in U.S. EPA, 1980a)

NAS (National Academy of Sciences, Food and Nutrition Board). 1980. Recommended dietary allowances, 9th rev. ed. NRC, NAS, Washington, DC. p. 162. (Cited in U.S. EPA, 1980a)

Natusch, D.F.S., J.R. Wallace and C.A. Evans, Jr. 1974. Toxic trace elements: Preferential concentration respirable particles. Science. 183: 202-204.

NCI (National Cancer Institute). 1978. NCI carcinogenesis bioassay experimental design status report for selenium sulfide (preliminary data). NCI Contract No. 702209. (Cited in U.S. EPA, 1980a)

Nelson, A.A., et al. 1943. Liver tumors following cirrhosis caused by selenium in rats. Cancer Res. 3: 230. (Cited in U.S. EPA, 1980a)

Page, G.W. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ. Sci. Technol. 15: 1475-1481.

Palmer, I.S., R.C. Arnold, C.W. Carlson. 1973. Toxicity of various selenium derivatives to chick embryos. Poult. Sci. 52: 1841.

Palmer, I.S. and O.E. Olson. 1979. Partial prevention by cyanide of selenium poisoning in rats. Biochem. Biophys. Res. Commun. 90: 1379. (Cited in Levander, 1982)

Palmer, I.S., O.E. Olson, A.W. Halverson, R. Miller and C. Smith. 1980. Isolation of factors in linseed oil meal protective against chronic selenosis in rats. J. Nutr. 110: 145. (Cited in Levander, 1982)

Parizek, J. 1964. Vascular changes at sites of oestrogen biosynthesis produced by parenteral injection of cadmium salts: The destruction of the placenta by cadmium salts. J. Reprod. Fert. 7: 263-265. (Cited in U.S. EPA, 1980a)

Parizek, J., I. Ostadalova, I. Benes and A. Babicky. 1968. Pregnancy and trace elements: The protective effect of compounds of an essential trace element - selenium - against the peculiar toxic effects of cadmium during pregnancy. J. Reprod. Fert. 16: 507-509. (Cited in U.S. EPA, 1980a)

Parizek, J., et al. 1971. The detoxifying effects of selenium. Interrelations between compounds of selenium and certain metals. In: Newer Trace Elements in Nutrition, W. Mertz and W.E. Cornatzer, Ed. Marcel Dekker, NY. p. 85.

Paton, G.R. and A.C. Allison. 1972. Chromosome damage in human cell cultures induced by metal salts. Mutat. Res. 16: 332-336. (Cited in U.S. EPA, 1980a)

Robertson, D.S.F. 1970. Selenium, a possible teratogen? Lancet. 1: 518-519. (Cited in U.S. EPA, 1980a)

Rosenfeld, I. and O.A. Beath. 1964. Selenium. Geobotany, Biochemistry, Toxicity, and Nutrition. Academic Press, NY. (Cited in U.S. EPA, 1980a)

Rudert, C.P. and A.R. Lewis. 1978. The effect of potassium cyanide on the occurrence of nutritional myopathy in lambs. Rhod. J. Agric. Res. 16: 109. (Cited in Levander, 1982)

Rusiecki, W. and J. Brzezinski. 1966. Influence of sodium selenate on acute thallium poisonings. Acta. Pol. Pharmacol. 23: 69. (Cited in U.S. EPA, 1980a)

Schroeder, H.A. 1967. Effects of selenate, selenite and tellurite on the growth and early survival of mice and rats. J. Nutr. 92: 334-338. (Cited in U.S. EPA, 1980a)

Schroeder, H.A. and M. Mitchener. 1971a. Selenium and tellurium in rats: Effect on growth, survival, and tumors. J. Nutr. 101: 1531. (Cited in U.S. EPA, 1980a)

Schroeder, H.A., M. Mitchener. 1971b. Toxic effects of trace elements on the reproduction of rats and mice. Arch. Environ. Health. 23: 102.

Schroeder, H.A. and M. Mitchener. 1972. Selenium and tellurium in mice: Effects on growth, survival, and tumors. Arch. Environ. Health. 24: 66. (Cited in U.S. EPA, 1980a)

Schroeder, H.A., D.V. Frost, J.J. Balassa. 1970. Essential trace metals in man: Selenium. J. Chron. Dis. 23: 227.

Scott, M.L., G. Olson, L. Krook and W.R. Brown. 1967. Selenium-responsive myopathies of myocardium and of smooth muscle in the young poult. J. Nutr. 91: 573. (Cited in Levander, 1982)

Sentein, P. 1967. Action de derives du selenium (seleniates et selenites) comparee a celle d'acides divers (crotonique, acetique, citrique et phosphorique) sur les mitoses de segmentation. Chromasoma (Berl.) 23: 95-136. (Cited in U.S. EPA, 1980a).

Shamberger, R.J., D.V. Frost. 1969. Possible protective effect of selenium against human cancer. Can. Med. Assoc. J. 100: 682.

Shamberger, R.J. and G. Rudolph. 1966. Protection against cocarcinogenesis by antioxidants. Experientia. 22: 116.

Shamberger, R.J. and C.E. Willis. 1971. Selenium distribution and human cancer mortality. Crit. Rev. Clin. Lab. Sci. 2: 211. (Cited in U.S. EPA, 1980a)

Shamberger, R.J., et al. 1972. Antioxidants in cereals and in food preservatives and declining gastric cancer mortality. Cleveland Clin. 39: 119. (Cited in U.S. EPA, 1980a)

Shamberger, R.J., et al. 1973. Antioxidants and cancer. I. Selenium in the blood of normal and cancer patients. J. Natl. Cancer Inst. 50: 863. (Cited in U.S. EPA, 1980a)

Shapiro, J.R. 1972. Selenium and carcinogenesis: A review. Ann. N.Y. Acad. Sci. 192: 215.

Shapiro, J.R. 1973. Selenium compounds in nature and medicine: Selenium and human biology. In: Organic Selenium Compounds: Their Chemistry and Biology, D.L. Klayman and W.H.H. Guenther, Ed. John Wiley and Sons, Inc., NY. (Cited in U.S. EPA, 1980a)

Smith, M.I. 1939. Public Health Report 54, 1441. (Cited in Underwood, 1977; U.S. EPA, 1983a)

Smith, M.I., et al. 1936. The selenium problem in relation to public health. A preliminary survey to determine the possibility of selenium intoxication in the rural population living on seleniferous soil. U.S. Pub. Health Rep. 51: 1496. (Cited in U.S. EPA, 1980a)

Tank, G. and C.A. Storvick. 1960. Title not provided. J. Dent. Res. 39: 473. (Cited in Glover, 1967; U.S. EPA, 1983a)

Thomson, C.D. and R.D.H. Stewart. 1973. Metabolic studies of (^{75}Se) selenomethionine and (^{75}Se) selenite in the rat. Br. J. Nutr. 30: 139. (Cited in U.S. EPA, 1980a)

Thomson, C.D. and R.D.H. Stewart. 1974. The metabolism of (^{75}Se) selenite in young women. Br. J. Nutr. 32: 47. (Cited in U.S. EPA, 1980a)

Thomson, C.D., et al. 1975. Metabolic studies of (^{75}Se) selenocystine and (^{75}Se) selenomethionine in the rat. Br. J. Nutr. 34: 501. (Cited in U.S. EPA, 1980a)

Ting, K.P. and G.W.R. Walker. 1969. The distributive effect of selenoamino acid treatment on crossing-over in Drosophila melanogaster. Genetics. 61: 141-151. (Cited in U.S. EPA, 1980a)

Tinsley, I.J., et al. 1967. Selenium toxicity in rats. I. Growth and longevity. In: Selenium in Biomedicine, O.H. Muth, Ed. Proc. 1st Intl. Symp., Oregon State University, 1966. AVI Publishing Co., Westport, CT. p. 141. (Cited in U.S. EPA, 1980a)

Underwood, E.J. 1977. Trace Elements in Human and Animal Nutrition, 4th ed. Academic Press, New York. p. 302-346.

U.S. EPA. 1980a. Ambient Water Quality Criteria for Selenium. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-070. NTIS PB 81-117814.

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Quality Criteria. Federal Register. 45: 79347-79357.

U.S. EPA. 1983a. Reportable Quantity for Selenium (and Compounds). Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983b. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Acceptable Daily Intakes for Volatile Organic Chemicals. Inorganic Chemicals and Synthetic Organic Chemicals. Criteria and Standards Division, Office of Drinking Water. (Federal Register draft)

Vesce, C.A. 1974. Intossicazione spermentale da selenio. Intossicazione Sperimentale da Selenio, Folia Med. (Ital.) 33: 209. (Cited in U.S. EPA, 1980a)

Volgarev, M.N., L.A. Tscherkes. 1967. Further studies in tissue changes associated with sodium selenate. In: Selenium in Biomedicine, O.H. Muth, Ed. Proc. 1st Intl. Symp., Oregon State University, 1966. AVI Publishing Co., Westport, CT. p. 179-184. (Cited in Harr, 1978)

Wahlstrom, R.C. and O.E. Olson. 1958. The relation of prenatal and preweaning treatment to the effect of arsanilic acid on Se poisoning. J. Anim. Sci. 18: 578. (Cited in U.S. EPA, 1980a)

Walker, G.W.R. and A.M. Bradley. 1969. Interacting effects of sodium monohydrogenarsenate and selenocystine on crossing over in Drosophila melanogaster. Can. J. Genet. Cytol. 11: 677-688. (Cited in U.S. EPA, 1980a)

Weast, R.C. 1980. CRC Handbook of Chemistry and Physics, 61st ed. CRC Press, Boca Raton, FL.

Wedderburn, J.F. 1972. Selenium and cancer. New Zealand Vet. J. 20: 56. (Cited in U.S. EPA, 1980a)

Weisberger, A.S. and L.G. Suhrlaud. 1956a. Studies on anologies of L-cysteine and L-cystine. II. The effect of selenium cystine on Murphy lymphosarcoma tumor cells in the rat. Blood. 11: 11-18. (Cited in Shapiro, 1972)

Weisberger, A.S. and L.G. Suhrlaud. 1956b. Studies on anologies of L-cysteine and L-cystine. III. The effect of selenium cystine on leukemia in the rat. Blood. 11: 19. (Cited in Shapiro, 1972)

Weisberger, A.S., L.G. Suhrlaud, J. Seiffer. 1956. Studies on analogies of L-cysteine and L-cystine. I. Some structural requirements for inhibiting the incorporation of radioactive L-cystine by leukocytes. Blood. 11: 1-10. (Cited in Shapiro, 1972)

Yang, G., W. Shuzhen, R. Zhou, S. Sun. 1983. Endemic selenium intoxication of humans in China. Am. J. Clin. Nutr. 37: 872-888.

Young, V.R., A. Nahapetian and M. Janghorbani. 1982. Selenium bioavailability with reference to human nutrition. Am. J. Clin. Nutr. 35(5): 1076-1088.

APPENDIX

Summary Table for Selenium and Compounds

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS				ND	
AIC	human	0.1 mg/m^3	none	0.07 mg/day	Glover, 1967
Oral					
AIS	rat	3.2 ppm diet (0.16 mg/kg/day)	none	0.224 mg/day	Halverson et al., 1966
AIC	human	3.2 mg/day from diet of seleniferous foodstuffs	loss of hair, nails, dermatitis nemomuscular dysfunction	0.21 mg/day	Yang et al. 1983; U.S. EPA, 1985
Maximum composite score	mouse	3 ppm in drinking water (0.51 mg/kg/day) for 3 generations (RV_d=4.9)	increased neonatal mortality (RV_e=10)	49	Schroeder and Mitchener, 1971b; U.S. EPA, 1983a

ND = Not derived